IN THE MATTER OF an Application
for a German Patent
filed under 103 27 472.3, and
IN THE MATTER OF an Application
for Patent in U.S.A.
filed under No. 10/535,474

I, Dr. Dietmar Forstmeyer,
attorney to BOETERS & LIECK, of Oberanger 32, D-80331 Muenchen, Germany, do solemnly and sincerely declare that I am conversant with the English and German languages and am a competent translator thereof, and that the following is, to the best of my knowledge and belief, a true and correct translation of the German Patent Application filed under 103 27 472.3 by R & D Pharmaceuticals GmbH.

DECLARED:

THIS 6th DAY OF August 2007

D. Forstmeyer

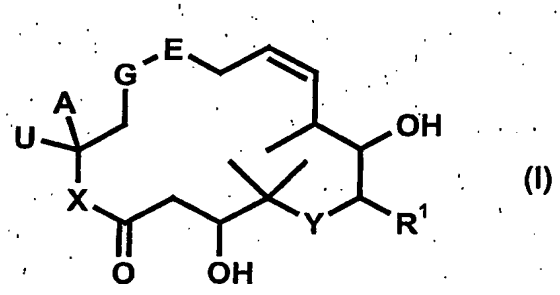
Dr. Dietmar Forstmeyer

Novel Macrocycles for the treatment of cancer

Epothilones (DE4138042) are natural products with extraordinary biological activity, e.g. as inhibitors of mitosis, microtubuli-modifying agents, cytotoxica or fungizides. Especially, they possess Paclitaxel-like properties and exceed Paclitaxel (Taxol®) in some tests in activity. Some derivatives are currently undergoing clinical trials for the cure of cancer diseases (Nicolaou et al. Angew. Chem. Int. Ed. 1998, 37, 2014-2045; Flörsheimer et al. Expert Opin. Ther. Patents 2001, 11, 951-968).

The object of the present invention was to provide new epothilone-like derivatives having an improved profile regarding their preclinical and clinical development potential.

The present invention relates to compounds of general Formula (I):



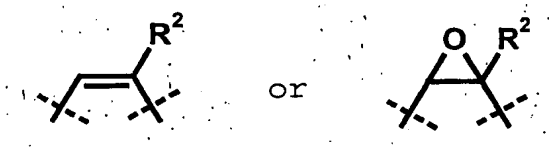
(I)

wherein

A is a C_1-C_4 alkyl or C_1-C_4 heteroalkyl residue,

U is an optionally substituted heteroaryl or a heteroarylalkyl residue,

G-E is selected from the following groups,



wherein R^2 is a hydrogen atom or a C_1-C_4 alkyl group,

R^1 is a C_1-C_4-alkyl or a C_3-C_4-cycloalkyl group,

X is an oxygen atom or a group of formula NR^3, wherein R^3 is a hydrogen atom, an alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, heterocycloalkyl, aralkyl or a heteroarylalkyl residue and

Y is a sulphur atom or a group of formula CO, SO or SO_2,

or a pharmacologically acceptable salt, solvate, hydrate or a pharmacologically acceptable formulation thereof.

The expression alkyl refers to a saturated, straight-chain or branched hydrocarbon group that contains from 1 to 20 carbon atoms, preferably from 1 to 12 carbon atoms, especially preferred from 1 to 6 carbon atoms, for example a methyl, ethyl, propyl, isopropyl, isobutyl, *tert*-butyl, n-hexyl, 2,2-dimethylbutyl or n-octyl group.

The expressions alkenyl and alkynyl refer to at least

partially unsaturated, straight-chain or branched hydrocarbon groups that contain from 2 to 20 carbon atoms, preferably from 2 to 12 carbon atoms, especially from 2 to 6 carbon atoms, for example an ethenyl, allyl, acetylenyl, propargyl, isoprenyl or hex-2-enyl group. Preferably, alkenyl groups have one or two (especially one) double bond(s) and alkynyl groups have one or two (especially one) triple bond(s).

Furthermore, the terms alkyl, alkenyl and alkynyl refer to groups in which one or more hydrogen atoms have been replaced by a halogen atom (preferably F or Cl) such as, for example, a 2,2,2-trichloroethyl or a trifluoromethyl group.

The expression heteroalkyl refers to an alkyl, alkenyl or alkynyl group in which one or more (preferably 1, 2 or 3) carbon atoms have been replaced by an oxygen, nitrogen, phosphorus, boron, selenium, silicon or sulphur atom (preferably oxygen, sulphur or nitrogen). The expression heteroalkyl furthermore refers to a carboxylic acid or to a group derived from a carboxylic acid such as, for example, acyl, acylalkyl, alkoxycarbonyl, acyloxy, acyloxyalkyl, carboxyalkylamide or alkoxycarbonyloxy.

Examples of heteroalkyl groups are groups of formulae R^a-O-Y^a-, R^a-S-Y^a-, R^a-N(R^b)-Y^a-, R^a-CO-Y^a-, R^a-O-CO-Y^a-, R^a-CO-O-Y^a-, R^a-CO-N(R^b)-Y^a-, R^a-N(R^b)-CO-Y^a-, R^a-O-CO-N(R^b)-Y^a-, R^a-N(R^b)-CO-O-Y^a-, R^a-N(R^b)-CO-N(R^c)-Y^a-, R^a-O-CO-O-Y^a-, R^a-N(R^b)-C(=NR^d)-N(R^c)-Y^a-, R^a-CS-Y^a-, R^a-O-CS-Y^a-, R^a-CS-O-Y^a-, R^a-CS-N(R^b)-Y^a-, R^a-N(R^b)-CS-Y^a-,

R^a-O-CS-N(R^b)-Y^a-, R^a-N(R^b)-CS-O-Y^a-, R^a-N(R^b)-CS-N(R^c)-Y^a-, R^a-O-CS-O-Y^a-, R^a-S-CO-Y^a-, R^a-CO-S-Y^a-, R^a-S-CO-N(R^b)-Y^a-, R^a-N(R^b)-CO-S-Y^a-, R^a-S-CO-O-Y^a-, R^a-O-CO-S-Y^a-, R^a-S-CO-S-Y^a-, R^a-S-CS-Y^a-, R^a-CS-S-Y^a-, R^a-S-CS-N(R^b)-Y^a-, R^a-N(R^b)-CS-S-Y^a-, R^a-S-CS-O-Y^a-, R^a-O-CS-S-Y^a-, R^a being a hydrogen atom, a C_1-C_6alkyl, a C_2-C_6alkenyl or a C_2-C_6alkynyl group; R^b being a hydrogen atom, a C_1-C_6alkyl, a C_2-C_6alkenyl or a C_2-C_6alkynyl group; R^c being a hydrogen atom, a C_1-C_6alkyl, a C_2-C_6alkenyl or a C_2-C_6alkynyl group; R^d being a hydrogen atom, a C_1-C_6alkyl, a C_2-C_6alkenyl or a C_2-C_6alkynyl group and Y^a being a direct bond, a C_1-C_6alkylene, a C_2-C_6alkenylene or a C_2-C_6alkynylene group, each heteroalkyl group containing at least one carbon atom and it being possible for one or more hydrogen atoms to have been replaced by fluorine or chlorine atoms. Specific examples of heteroalkyl groups are methoxy, trifluoromethoxy, ethoxy, n-propyloxy, isopropyloxy, *tert*-butyloxy, methoxymethyl, ethoxymethyl, methoxyethyl, methylamino, ethylamino, dimethylamino, diethylamino, isopropylethylamino, methylaminomethyl, ethylaminomethyl, diisopropylaminoethyl, enol ether, dimethylaminomethyl, dimethylaminoethyl, acetyl, propionyl, butyryloxy, acetyloxy, methoxycarbonyl, ethoxycarbonyl, N-ethyl-N-methylcarbamoyl and N-methylcarbamoyl. Further examples of heteroalkyl groups are nitrile, isonitrile, cyanate, thiocyanate, isocyanate, isothiocyanate and alkylnitrile groups.

The expression cycloalkyl refers to a saturated or partially unsaturated (e.g. cycloalkenyl) cyclic group that contains one or more rings (preferably 1 or 2) forming a structure

containing from 3 to 14 carbon atoms, preferably from 3 to 10 (especially 3, 4, 5, 6 or 7) carbon atoms. The expression cycloalkyl refers furthermore to groups in which one or more hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH_2, =NH or NO_2 groups, thus, for example, cyclic ketones such as, for example, cyclohexanone, 2-cyclohexenone or cyclopentanone. Further specific examples of cycloalkyl groups are a cyclopropyl, cyclobutyl, cyclopentyl, spiro[4,5]decanyl, norbornyl, cyclohexyl, cyclopentenyl, cyclohexadienyl, decalinyl, cubanyl, bicyclo[4.3.0]nonyl, tetralin, cyclopentylcyclohexyl, fluorocyclohexyl or cyclohex-2-enyl group.

The expression heterocycloalkyl refers to a cycloalkyl group as defined above in which one or more (preferably 1, 2 or 3) ring carbon atoms have been replaced by an oxygen, nitrogen, silicon, selenium, phosphorus or sulphur atom (preferably oxygen, sulphur or nitrogen). A heterocycloalkyl group has preferably 1 or 2 ring(s) containing from 3 to 10 (especially 3, 4, 5, 6 or 7) ring atoms. The expression heterocycloalkyl refers furthermore to groups in which one or more hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH_2, =NH or NO_2 groups. Examples are a piperidyl, morpholinyl, urotropinyl, pyrrolidinyl, tetrahydrothiophenyl, tetrahydropyranyl, tetrahydrofuryl, oxacyclopropyl, azacyclopropyl or 2-pyrazolinyl group and also lactams, lactones, cyclic imides and cyclic anhydrides.

The expression alkylcycloalkyl refers to groups containing

both cycloalkyl and also alkyl, alkenyl or alkynyl groups in accordance with the above definitions, for example alkylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkyl and alkynylcycloalkyl groups. An alkylcycloalkyl group preferably contains a cycloalkyl group that contains one or two rings systems forming a structure having from 3 to 10 (especially 3, 4, 5, 6 or 7) carbon atoms, and one or two alkyl, alkenyl or alkynyl groups having 1 or 2 to 6 carbon atoms.

The expression heteroalkylcycloalkyl refers to alkylcycloalkyl groups as defined above in which one or more (preferably 1, 2 or 3) carbon atoms have been replaced by an oxygen, nitrogen, silicon, selenium, phosphorus or sulphur atom (preferably oxygen, sulphur or nitrogen). A heteroalkylcycloalkyl group preferably contains 1 or 2 ring systems having from 3 to 10 (especially 3, 4, 5, 6 or 7) ring atoms, and one or two alkyl, alkenyl, alkynyl or heteroalkyl groups having 1 or 2 to 6 carbon atoms. Examples of such groups are alkylheterocycloalkyl, alkylheterocycloalkenyl, alkenylheterocycloalkyl, alkynylheterocycloalkyl, heteroalkylcycloalkyl, heteroalkylheterocycloalkyl and heteroalkylheterocylcloalkenyl, the cyclic groups being saturated or mono-, di- or tri-unsaturated.

The expression aryl or Ar refers to an aromatic group that has one or more rings and is formed by a structure containing from 6 to 14 carbon atoms, preferably from 6 to 10 (especially 6) carbon atoms. The expression aryl (or Ar) refers furthermore to groups in which one or more hydrogen

atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, SH, NH_2 or NO_2 groups. Examples are a phenyl, naphthyl, biphenyl, 2-fluorophenyl, anilinyl, 3-nitrophenyl or 4-hydroxyphenyl group.

The expression heteroaryl refers to an aromatic group that has one or more rings and is formed by a ring system that contains from 5 to 14 ring atoms, preferably from 5 to 10 (especially 5 or 6) ring atoms, and contains one or more (preferably 1, 2, 3 or 4) oxygen, nitrogen, phosphorus or sulphur ring atoms (preferably O, S or N). The expression heteroaryl refers furthermore to groups in which one or more hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, SH, NH_2 or NO_2 groups. Examples are 4-pyridyl, 2-imidazolyl, 3-phenylpyrrolyl, thiazolyl, oxazolyl, triazolyl, tetrazolyl, isoxazolyl, indazolyl, indolyl, benzimidazolyl, pyridazinyl, quinolinyl, purinyl, carbazolyl, acridinyl, pyrimidyl, 2,3´-bifuryl, 3-pyrazolyl and isoquinolinyl groups.

The expression aralkyl refers to groups containing both aryl and also alkyl, alkenyl, alkynyl and/or cycloalkyl groups in accordance with the above definitions, such as, for example, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, arylcycloalkenyl, alkylarylcycloalkyl and alkylarylcycloalkenyl groups. Specific examples of aralkyls are toluene, xylene, mesitylene, styrene, benzyl chloride, o-fluorotoluene, 1H-indene, tetralin, dihydronaphthalene, indanone, phenylcyclopentyl, cumene, cyclohexylphenyl, fluorene and indan. An aralkyl group preferably contains

one or two aromatic ring systems (1 or 2 rings) containing from 6 to 10 carbon atoms and one or two alkyl, alkenyl and/or alkynyl groups containing 1 or 2 to 6 carbon atoms and/or a cycloalkyl group containing 5 or 6 ring carbon atoms.

The expression heteroaralkyl refers to an aralkyl group as defined above in which one or more (preferably 1, 2, 3 or 4) carbon atoms have been replaced by an oxygen, nitrogen, silicon, selenium, phosphorus, boron or sulphur atom (preferably oxygen, sulphur or nitrogen), that is to say to groups containing both aryl or heteroaryl and also alkyl, alkenyl, alkynyl and/or heteroalkyl and/or cycloalkyl and/or heterocycloalkyl groups in accordance with the above definitions. A heteroaralkyl group preferably contains one or two aromatic ring systems (1 or 2 rings) containing 5 or 6 to 10 carbon atoms and one or two alkyl, alkenyl and/or alkynyl groups containing 1 or 2 to 6 carbon atoms and/or a cycloalkyl group containing 5 or 6 ring carbon atoms, 1, 2, 3 or 4 or those carbon atoms having been replaced by oxygen, sulphur or nitrogen atoms.

Examples are arylheteroalkyl, arylheterocycloalkyl, arylheterocycloalkenyl, arylalkylheterocycloalkyl, arylalkenylheterocycloalkyl, arylalkynylheterocycloalkyl, arylalkylheterocycloalkenyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylcycloalkyl, heteroarylcycloalkenyl, heteroarylheterocycloalkyl, heteroarylheterocycloalkenyl, heteroarylalkylcycloalkyl, heteroarylalkylheterocycloalkenyl, heteroaryl-

heteroalkylcycloalkyl, heteroarylheteroalkylcycloalkenyl and heteroarylheteroalkylheterocycloalkyl groups, the cyclic groups being saturated or mono-, di- or tri-unsaturated. Specific examples are a tetrahydroisoquinolyl-, benzoyl-, 2- or 3-ethylindolyl-, 4-methylpyridino-, 2-, 3- or 4-methoxyphenyl-, 4-ethoxyphenyl-, 2-, 3- or 4-carboxyphenyl-alkyl group.

The expressions cycloalkyl, heterocycloalkyl, alkyl-cycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl refer to groups in which one or more hydrogen atoms of such groups have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH_2, =NH or NO_2 groups.

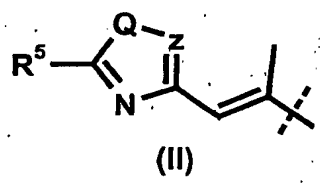
The expression "optionally substituted" refers to groups in which one or more hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH_2, =NH or NO_2 groups. The expression refers furthermore to groups that are substituted by unsubstituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_{10}cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_1-C_9heteroaryl, C_7-C_{12}aralkyl or C_2-C_{11}heteroaralkyl groups.

Owing to their substitution, compounds of formula (I) may contain one or more centres of chirality. The present invention therefore includes both all pure enantiomers and all pure diastereoisomers and also mixtures thereof in any mixing ratio. The present invention moreover also includes all *cis/trans*-isomers of the compounds of the general

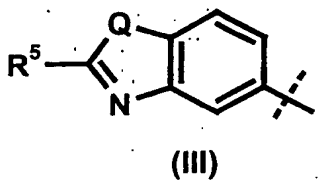
formula (I) and also mixtures thereof. The present invention moreover includes all tautomeric forms of the compounds of formula (I).

Preferred are compounds of formula (I), wherein U is a group of the formula $-C(CH_3)=CHR^4$ or $-CH=CHR^4$, wherein R^4 is an optionally substituted heteroaryl or heteroarylalkyl residue.

Further preferred are compounds of formula (I), wherein U shows the general formula (II) or (III):



(II)



(III)

wherein Q is a sulphur atom, an oxygen atom or a group of formula NR^6, wherein R^6 is a hydrogen atom, a C_1-C_4 alkyl group or a C_1-C_4 heteroalkyl group, z is a nitrogen atom or a CH group and R^5 is a group of formula OR^7 or NHR^7, an alkyl, alkenyl, alkynyl or a heteroalkyl group (preferably a group of formula CH_2OR^7 or CH_2NHR^7), wherein R^7 is a hydrogen atom, a C_1-C_4 alkyl group or a C_1-C_4 heteroalkyl group (especially a hydrogen atom).

Especially preferred, z is a CH group.

Again preferred are compounds of formula (I) wherein Q is a sulphur atom or an oxygen atom.

Especially preferred are compounds of formula (I) wherein R^5 is a group of formula CH_3, CH_2OH or CH_2NH_2.

Further preferred are compounds of formula (I), wherein X is an oxygen atom or a NH group.

Again preferred, R^1 is a methyl or an ethyl group; especially preferably a methyl group.

Further preferred, A is a group of formula CH_3, CF_3 or COOH.

Moreover preferred, R^2 is a group of formula CH_3 or CF_3.

Again preferred, Y is a C=O group.

Examples of pharmacologically acceptable salts of compounds of formula (I) are salts (or mixed salts) of physiologically acceptable mineral acids, such as hydrochloric acid, sulphuric acid and phosphoric acid; or salts of organic acids, such as methanesulphonic acid, p-toluenesulphonic acid, lactic acid, acetic acid, trifluoroacetic acid, citric acid, succinic acid, fumaric acid, maleic acid and salicylic acid. Compounds of formula (I) can be solvated, especially hydrated. The hydration may take place, for example, during the preparation process or as a consequence of the hygroscopic nature of the initially anhydrous compounds of formula (I). If the compounds of Formula (I) contain asymmetric C-atoms they may be present either as achiral compounds, mixtures of diastereomers, mixtures of

enantiomers or as optically pure compounds. Furthermore, the present invention also includes all cis/trans isomers of the present compounds of general formula (I) and also mixtures thereof.

The pharmaceutical compositions according to the present invention comprise at least one compound of formula (I) as active ingredient and optionally carrier substances and/or adjuvants.

The pro-drugs (see, e.g. R. B. Silverman, Medizinische Chemie, VCH Weinheim, 1995, Chapter 8, S. 361ff), which are also an object of the present invention, consist of a compound of formula (I) and at least one pharmacologically acceptable protecting group that is removed under physiological conditions, for example an alkoxy, aralkyloxy, acyl or acyloxy group, such as, for example, an ethoxy, benzyloxy, acetyl or acetyloxy group.

The therapeutic use of the compounds of formula (I), of their pharmacologically acceptable salts and solvates and hydrates and also formulations and pharmaceutical compositions also lies within the scope of the present invention.

The use of those active ingredients in the preparation of medicaments for the treatment of cancer diseases is also an object of the present invention. In general, compounds of Formula (I) will be administered by using the known and acceptable modes known in the art, either alone or in

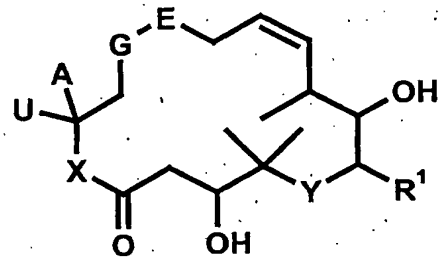
combination with any other therapeutic agent. Such therapeutically useful agents can be administered by one of the following routes: oral, e.g. as dragees, coated tablets, pills, semisolids, soft or hard capsules, solutions, emulsions or suspensions; parenteral e.g. as an injectable solution; rectal as suppositories; by inhalation e.g. as a powder formulation or spray, transdermal or intranasal. For the production of such tablets, pills, semisolids, coated tablets, dragees and hard gelatin capsules the therapeutically useful product may be mixed with pharmaceutically inert, inorganic or organic excipients e.g. with lactose, sucrose, glucose, gelatin, malt, silica gel, starch or derivatives thereof, talc, stearic acid or their salts, dried skim milk, and the like. For the production of soft capsules one may use excipients as e.g. vegetable oils, petroleum, animal or synthetic oils, wax, fat, polyols. For the production of liquid solutions and syrups one may use excipients as e.g. water, alcohols, aqueous saline, aqueous dextrose, polyols, glycerin, vegetable oils, petroleum, animal or synthetic oils. For suppositories one may use excipients as e.g. vegetable oils, petroleum, animal or synthetic oils, wax, fat and polyols. For aerosol formulations one may use compressed gases suitable for this purpose, as e.g. oxygen, nitrogen, noble gases and carbon dioxide. The pharmaceutically useful agents may also contain additives for conservation, stabilization, emulsifiers, sweeteners, flavourings, salts to change the osmotic pressure, buffers, coating additives and antioxidants.

Combinations with other therapeutic agents may include other therapeutically useful agents that are commonly used to treat cancer diseases.

For the treatment of cancer diseases the dose of the biologically active compound according to the present invention may vary within broad limits and can be adjusted to the individual needs. In general a dose of 0.1 microgram to 100 milligram per kilogram body weight per day is appropriate, with a preferred dose of 10 micrograms to 25 milligrams/kilogram per day. In appropriate cases the dose may be also higher or lower than given above.

Claims

1. Compounds of general Formula (I)



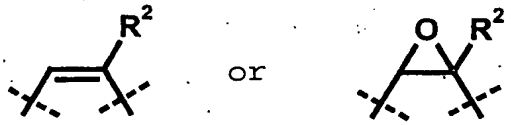
(I)

wherein

A is a C_1-C_4 alkyl or a C_1-C_4 heteroalkyl residue,

U is an optionally substituted heteroaryl or a heteroarylalkyl residue,

G-E is selected from the following groups,



wherein R^2 is a hydrogen atom or a C_1-C_4 alkyl group,

R^1 is a C_1-C_4-alkyl or a C_3-C_4-cycloalkyl group,

X is an oxygen atom or a group of formula NR^3, wherein R^3 is a hydrogen atom, an alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, alkyl-

cycloalkyl, heteroalkylcycloalkyl, heterocycloalkyl, aralkyl or heteroarylalkyl residue and

Y is a sulphur atom or a group of formula CO, SO or SO_2,

or a pharmacologically acceptable salt, solvate, hydrate or a pharmaceutically acceptable formulation thereof.

2. Compounds of formula (I), wherein Y is a C=O group.

3. Compounds according to claim 1 or 2, wherein X is an oxygen atom.

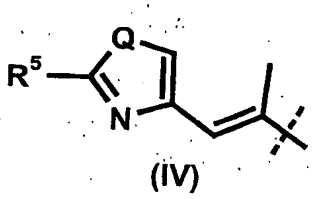
4. Compounds according to anyone of claims 1 to 3, wherein R^1 is a methyl group.

5. Compounds according to anyone of claims 1 to 4, wherein A is a group of formula CH_3, CF_3 or COOH.

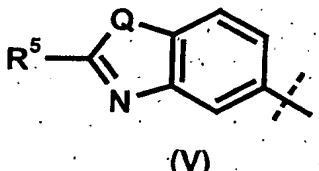
6. Compounds according to anyone of claims 1 to 5, wherein R^2 is a group of formula CH_3 or CF_3.

7. Compounds according to anyone of claims 1 to 6, wherein U is a group of formula $-C(CH_3)=CHR^4$ or $-CH=CHR^4$, wherein R^4 is an optionally substituted heteroaryl or heteroarylalkyl residue.

8. Compounds according to anyone of claims 1 to 7, wherein U shows the general formula (IV) or (V),



(IV)



(V)

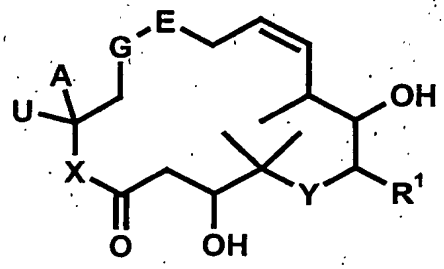
wherein Q is a sulphur atom or an oxygen atom and R^5 is a group of formula CH_3, CH_2OH or CH_2NH_2.

9. Pharmaceutical composition containing a compound according to anyone of claims 1 to 8 and optionally carriers and/or adjuvants.

10. Use of a compound or a pharmaceutical composition according to any one of claims 1 to 9 for the treatment of cancer diseases.

Abstract

The present invention relates to novel macrocycles of general formula (I) and their use for the treatment of cancer diseases.



(I)